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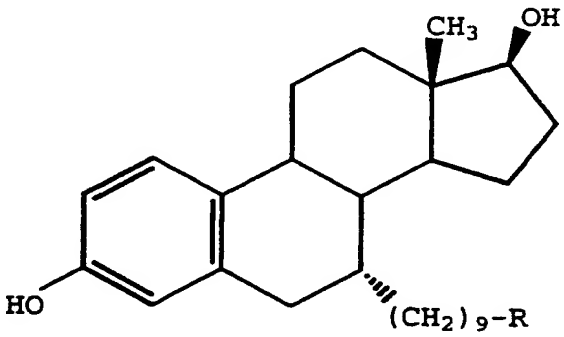
(54) Methods for minimizing bone loss

(57) The present invention provides a method for minimizing the bone loss effect of a compound of formula I



I

wherein R is $-CH_2CON(CH_3)$-n-$CH_2CH_2CH_2CH_3$ or $-SO(CH_2)_3CF_2CF_3$, or a pharmaceutically acceptable salt thereof, and wherein said formula I compound is administered to a mammal in need of treatment, comprising concurrently or sequentially administering to said mammal an effective amount of a compound of formula II

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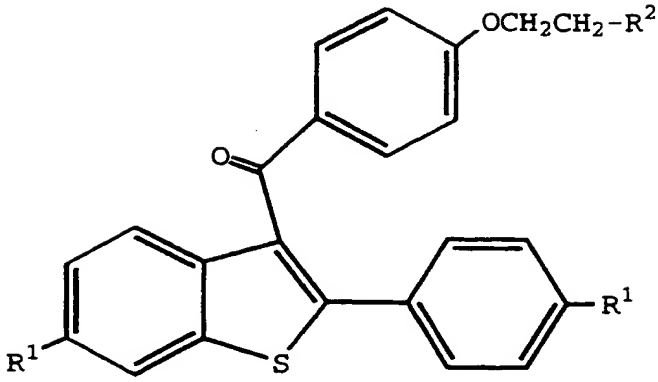


II

wherein

each R^1 is independently -H, -OH, -O(C_1-C_4 alkyl), -OCOC$_6$H$_5$, -OCO(C_1-C_6 alkyl), or -OSO$_2$(C_4-C_6 alkyl); and

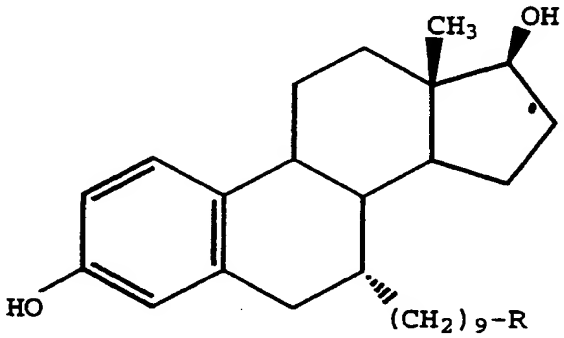
R^2 is 1-piperidinyl, 1-pyrrolidinyl, methyl-1-pyrrolidinyl, dimethyl-1-pyrrolidinyl, 4-morpholino, dimethylamino, diethylamino, or 1-hexamethyleneimino; or a pharmaceutically acceptable salt thereof.

Also provided is a method for minimizing bone loss induced by the administration of a formula I compound comprising concurrently or sequentially administering a bone anabolic agent. Pharmaceutical compositions are also provided.

Description

The present invention relates to the fields of pharmacology and pharmaceutical chemistry, and provides methods for minimizing the bone loss effect induced by the administration of certain pharmaceutical agents, and pharmaceutical compositions therefor.

Compounds of formula I

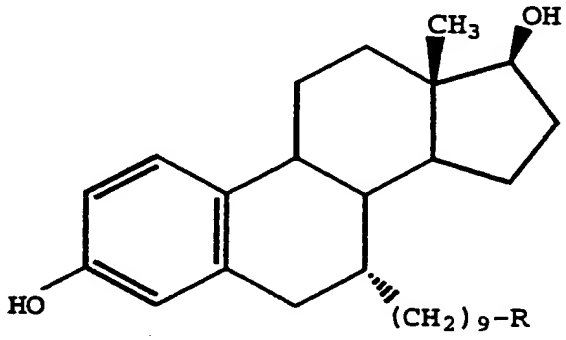


I

wherein R is $-CH_2CON(CH_3)$-n-$CH_2CH_2CH_2CH_3$ or $-SO(CH_2)_3CF_2CF_3$, or a pharmaceutically acceptable salt thereof are known in the art as ICI-164384 and ICI-182780, respectively (see, e.g., European Publication 138504; and U.S. Pat. No. 4,659,516). These steroidal compounds have been characterized as Type III antiestrogens by McDonald, D.P., et al., (Steroid Receptor and Anti-Hormones Symposia, New York Acad. Sci., Dallas, TX, Sept. 20-23, 1994), and have further been classified as "pure" antiestrogens which are devoid of agonist activity. As such, compounds of formula I bind to the estrogen receptor (ER) with high affinity, thus blocking the binding of estrogen and its metabolites. These compounds also appear to inhibit ER dimerization and facilitate cytoplasmic accumulation of ER leading to rapid degradation resulting in loss of immunodetectable protein. Accordingly, these compounds are understood to be promising therapeutic agents for the treatment of inter alia, breast cancer [see, e.g., Howell, A., Lancet, 345:29-30 (1995)] endometriosis, uterine fibroids, and other estrogen-induced maladies.

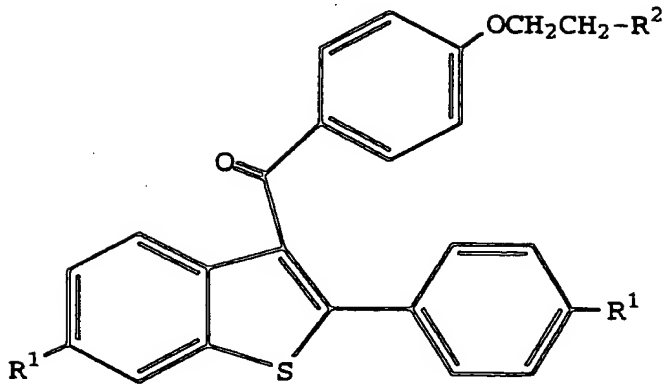
Unfortunately, compounds of formula I are devoid of estrogen agonist activity and, thus, induce a state similar to that seen in postmenopausal women. More particularly, these compounds are capable of inducing bone loss such as seen with osteoporosis. The induction of a postmenopausal state and, particularly, the induction of bone loss, is one of the most limiting side-effects of these compounds when administered for estrogen-induced maladies in mammals. It, therefore, would be of great value to be able to take advantage of the distinct antiestrogenic activity of formula I compounds while minimizing the negative side effects associated with the use of the compounds via the sequential or concurrent administration of another pharmaceutical agent.

The present invention, therefore, provides a method of minimizing the bone loss effect of a compound of formula I



I

wherein R is $-CH_2CON(CH_3)$-n-$CH_2CH_2CH_2CH_3$ or $-SO(CH_2)_3CF_2CF_3$, or a pharmaceutically acceptable salt thereof, and wherein said formula I compound is administered to a mammal in need of treatment, comprising concurrently or sequentially administering to said mammal an effective amount of a compound of formula II



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each R^1 is independently -H, -OH, -O(C_1-C_4 alkyl), -OCOC$_6$H$_5$, -OCO(C_1-C_6 alkyl), or -OSO$_2$(C_4-C_6 alkyl); and

R^2 is 1-piperidinyl, 1-pyrrolidinyl, methyl-1-pyrrolidinyl, dimethyl-1-pyrrolidinyl, 4-morpholino, dimethylamino, diethylamino, or 1-hexamethyleneimino; or a pharmaceutically acceptable salt thereof, are well known in the art and can be prepared according to established procedures, such as those detailed in U.S. Pat. Nos. 4,133,814; 4,418,068; and 4,380,635, each of which is incorporated by reference.

Compounds of formula II, particularly raloxifene, in which each R^1 is -OH and R^2 is 1-piperidinyl, has been classified by McDonald, supra, as a type II antiestrogen. Compounds of formula II also are recognized in the art as selective estrogen receptor modulators (SERMs), or tissue selective estrogen receptor agonists/antagonists. As such, the compounds of formula II are recognized as nuclear regulatory molecules. More particularly, raloxifene has been shown to bind to estrogen receptors and originally was demonstrated to have antiestrogenic activity because it blocked the ability of estrogen to activate uterine tissue and estrogen-dependent cancers. Indeed, raloxifene does block the action of estrogen in some cells but, in other cell types, it activates the same genes as estrogen activates and displays the same pharmacology. As a type II antiestrogen, SERM, raloxifene, and its analogs defined above as compounds of formula II, are tissue selective antiestrogens with mixed agonist-antagonist properties.

Although compounds of formulae I and II generally compete for and utilize the same receptors, the pharmacological outcome of administration of these distinct agents is not easily predicted, and is distinct to each.

Bone anabolic agents are those agents which are known in the art to build bone by increasing the production of bone matrix protein. Such anabolic agents include, for example, the various forms of parathyroid hormone (PTH) such as naturally occurring PTH (1-84), PTH (1-34), analogs thereof, and the like, which are prepared via well known procedures.

As used herein, "bone loss" means a reduction of bone mineral density of cancellous bone, which frequently is a side-effect of formula I compound administration to mammals, and the term "minimize", or a derivative thereof, contemplates partial or complete inhibition and/or repair of a compound of formula I-induced bone loss.

The methods of the present invention can be tailored to counter the bone loss effect induced by the administration of a formula I compound. For example, when administration of a formula I compound is first initiated, particularly as an acute treatment, it is preferred to coadminister a compound of formula II, especially the hydrochloride salt of raloxifene, to counteract the potential bone loss. When administration of a formula I compound will be for the treatment of a chronic malady (e.g., endometriosis; cancer adjuvant following surgery), a formula II compound, preferably raloxifene hydrochloride, and an anabolic bone agent, particularly PTH (1-84) or PTH (1-34), may be coadministered at the time treatment with a formula I compound is initiated, and throughout the course of therapy. However, if a formula I compound is administered for a chronic malady without the coadministration of a formula II compound, a bone anabolic agent may be coadministered with, or following, multiple courses of therapy with a formula I compound. The particular method of the present invention which would optimize the minimization of bone loss induced by the administration of a formula I compound is, therefore, dictated by the duration of a formula I compound's course of therapy, and when administration of a compound of formula II, and/or a bone anabolic agent, is initiated relative to the commencement of therapy of a formula I compound. In essence, the attending physician is best suited to determine whether a formula II compound and/or a bone anabolic agent should be administered, and whether the administration of such agents should be concurrent or sequential to the administration of a formula I compound.

When administered sequentially, pharmaceutical formulations of compound of formulae I and II and bone anabolic agents are prepared by methods known by one of ordinary skill in the art.

Ingredient	Quantity (mg/capsule)
Formula I compound	0.1 - 1000
Starch, NF	0 - 650
Starch flowable powder	0 - 650
Silicone fluid 350 centistokes	0 - 15

Formulation 2: Raloxifene capsule

Ingredient	Quantity (mg/capsule)
Raloxifene HCl	10
Starch, NF	103
Starch flowable powder	225.3
Silicone fluid 350 centistokes	1.7

Formulation 3: Raloxifene capsule

Ingredient	Quantity (mg/capsule)
Raloxifene HCl	50
Starch, NF	150
Starch flowable powder	397
Silicone fluid 350 centistokes	3.0

The specific formulations above may be changed in compliance with the reasonable variations provided.
A tablet formulation is prepared using the ingredients below:

Formulation 6: Suspension

Ingredient	Quantity (mg/5 ml)
Formula I compound	25 - 1000 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 mg
Benzoic acid solution	0.10 mL
Flavor	q.v.
Color	q.v.
Purified water to	5 mL

The medicament is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor, and color are diluted with some of the water and added, with stirring. Sufficient water is then added to produce the required volume.

Composition 1: Intravenous Solution

Ingredient	Quantity
Formula I compound	50 mg
Formula II compound	50 mg
Isotonic saline	1000 mL

Composition 2: Intravenous Solution

Ingredient	Quantity
Formula I compound	50 mg
PTH (1-84) or (1-34)	0.1-1000 mg
Isotonic saline	1000 mL

pound when compared to a control group which has been continuously treated with a compound of formula II. Specifically, three groups of animals are chosen. The first group would be a no treatment control group. The second group would receive a S.C. dose of a formula I compound in an oily suspension every 21 days for six months. The third group would receive an alternating schedule of therapy consisting of a compound of formula I followed after 21 days with a daily dose of a formula II compound for 14 days. This protocol would be repeated for six months. At the end of the experiment, the bone mineral density is determined by DEXA (Dual Energy X-ray Analysis), demonstrating the bone loss efficacy of the coadministered compound of formula II.

Bone Loss V

Twenty to fifty women with diagnosed estrogen-dependent breast cancer are selected for the study. These women may be pre- or post-menopausal, have a WHO performance status of less than two, and have a life expectancy of greater than one year. Further, these women may or may not have had previous surgical intervention and should not have been treated with tamoxifene or other anti-cancer chemotherapeutic agents.

These patients are initially evaluated for their cancer status by techniques known in the art, (see, e.g., Howell, A., supra, and references cited therein). In addition, the patients are evaluated for bone status by monitoring bone mineral density by DEXA, urinary calcium, creatinine, hydroxyproline, and pyridinoline crosslinks.

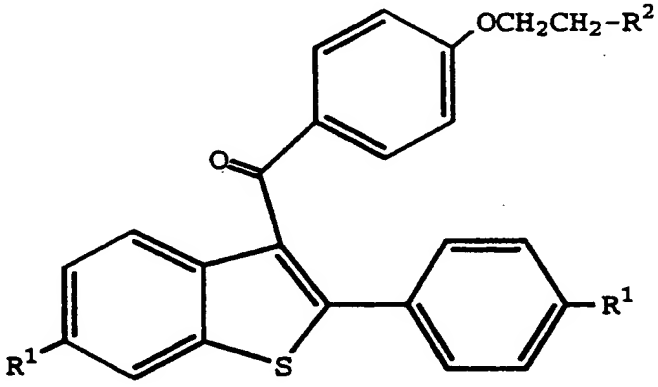
Patients are treated for cancer by monthly injection of an oily suspension of 100-250 mg of a formula I compound. During monthly visits to the attending physician, bone mineral density and the above bone markers are evaluated. Either immediately, or when bone loss reaches about 10% to 20% of the base line measurement, patients additionally receive 50-250 mg of raloxifene, P.O., for the remainder of the trial period. The duration of the present trial is one year.

This trial demonstrates the minimization of bone loss via administration of a formula I compound while not affecting the cancer efficacy of a formula I compound.

Alternatively, a bone anabolic agent, particularly PTH (1-84) or (1-34), can be administered in lieu of, or in addition to, the administration of a formula II compound.

Claims

1. The use of a compound of formula II



II

wherein

each R^1 is independently -H, -OH, -O(C_1-C_4 alkyl), -OCOC$_6$H$_5$, -OCO(C_1-C_6 alkyl), or -OSO$_2$(C_4-C_6 alkyl); and

R^2 is 1-piperidinyl, 1-pyrrolidinyl, methyl-1-pyrrolidinyl, dimethyl-1-pyrrolidinyl, 4-morpholino, dimethylamino, diethylamino, or 1-hexamethyleneimino; or a pharmaceutically acceptable salt thereof, in the preparation of a medicament useful for minimizing the bone loss effects of a compound of formula I